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10/534,043	03/30/2006	Nobuo Sakaguchi	4456-0104PUS1	2803

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EXAMINER
HAMA, JOANNE

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
07/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/534,043	SAKAGUCHI, NOBUO	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6 and 12-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of October 11, 2007 on April 10, 2008.

Claims 4, 7-11 are cancelled. Claims 1, 2, 5, 6, 12 are amended. Claims 13-19 are new.

Claims 1-3, 5, 6, 12-19 are under consideration.

Information Disclosure Statement

Applicant indicates that "Fujiwara et al." a typographical error and the author's name of reference CD on the IDS entered May 5, 2005 is "Fujimura et al." Applicant also provides a copy and translation of the relevant parts of Fujimura et al. The IDS submitted May 5, 2005 has been considered.

Withdrawn Rejections

35 USC § 112, 1st parag., Written Description

Applicant's arguments, see pages 6-7 of Applicant's response, filed April 10, 2008, with respect to the rejection of claims 1-6, 12 as lacking written description have been fully considered and are persuasive. Applicant has amended claim 1 such that the non-human mammal comprises a human or mouse GANP gene. The rejection of claims 1-3, 5, 6, 12 has been withdrawn. It is noted that the rejection of claim 4 is withdrawn as the claim has been cancelled.

35 USC § 112, 2nd parag.

Applicant's arguments, see page 8 of Applicant's response, filed April 10, 2008, with respect to the rejection of claim 6 have been fully considered. Upon further consideration, the rejection of claim 6 has been withdrawn as the preamble of claim 6 indicates that the claimed method is a method of making high affinity antibody and does not require that the antibody be isolated. The rejection of claim 6 has been withdrawn.

New/Maintained Objection/Rejections

Claim Objections

Claim 15 is newly objected to because of the following informalities: Claim 15 uses the word, "does". This appears to be a typographical error of the word, "dose". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 6, 12 remain rejected and new claims 13-19 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record, October 11, 2007.

Applicant's arguments filed April 10, 2008 have been fully considered but they are not persuasive.

Applicant indicates that it is clearly within the skill of a skilled artisan to generate mutants and that disclosure of how to generate mutants is not necessary to support the presently claimed invention. Further, Applicant insists that generating transgenic animals is routine and well within the skill of an ordinary artisan at the time that the instant application was filed. The Examiner has not provided evidence to the contrary. Applicant indicates that, "(a)s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112 is satisfied" (Applicant's response, pages 6-7). In response, this is not persuasive. With regard to Applicant indicating that making transgenic animals is routine in the art, the Examiner was not questioning whether an artisan was physically able to make transgenic animals. Rather, the art, see Office Action, October 11, 2007, pages 7-9, indicates that making transgenic animals with a predictable phenotype is not routine in the art. The claims encompass a wide variety of transgenic non-human mammalian species; however, the art teaches that there is unpredictability in overexpressing recombinant proteins in heterologous species of animals (e.g. see Jakel et al., 2004). As such, the claims are not enabled for the full scope of claimed non-human mammals in which to practice the claimed invention. As such, the rejection as it applies to this issue remains.

With regard to Applicant indicating that "(a)s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable

correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112 is satisfied," one method of making and using is not sufficient to practice the breadth of Applicant's claimed invention. In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." As discussed in the Office Action, October 11, 2008, pages 6-10, the claims encompass a wide variety of non-human mammals in which to practice the claimed invention. However, as described in the Office Action, there is unpredictability in expressing a protein of interest in a heterologous non-human mammal and obtaining an animal with a predictable phenotype. As such, the claims remain rejection regarding this issue.

With regard to the scope of ES cells used to make the claimed non-human mammalian species (see claim 3), the art has indicated that using ES cells other than mouse to make transgenic mammals is not routine in the art (see Murray et al., 1999; Office Action, October 11, 2007, pages 10-11). No response has been provided regarding this issue and thus, the rejection as it applies to this issue remains.

With regard to the Office Action referring to the specification for teaching that the transgenic GANP mice express high affinity antibody, the Office Action has indicated that the results described in the specification does not provide guidance that the antibodies made by the claimed mice are necessarily high affinity antibodies. Rather, the results left open the interpretation that the transgenic GANP mice could also be interpreted to be producing large amounts of low affinity antibody. The Office Action also looked at other data described in the specification to determine whether the transgenic GANP mice also produced high affinity antibody. With regard to the specification indicating particular sites that were mutated in the V_H186.2 region and that these mutations were indicative that the transgenic GANP mice would express high affinity antibody, the specification provides no correlation between mutation sites and production of high affinity antibody. The specification teaches that different lines of mice had different mutations in the V_H186.2 region and given this teaching, an artisan cannot reasonably predict which of the mutations are correlated to high affinity binding. Similarly, it cannot be correlated whether any of the mutations in the V_H186.2 region result in low affinity antibodies. Because Applicant has not provided any response

regarding this issue, the issue regarding the enablement of the claimed non-human transgenic GANP mammals to produce high affinity antibodies remains.

Thus, the rejections are maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-19 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-19 use the phrase, "operably limited to a human IgG enhancer, or its progeny." It is unclear what this phrase means. The Examiner looked through the specification for guidance as to how this phrase is defined and cannot find any guidance. First, it is unclear what a progeny of a human IgG enhancer is. Second, it is unclear how a GANP gene is operably limited to a human IgG enhancer. Did Applicant intend to mean, "operably linked?"

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kuwahara et al., 2000, Blood, 95: 2321-2328, previously cited, in view of Jaenisch, 1988, Science, 240: 1468-1474, previously cited, Maas et al., 1999, The Journal of Immunology, 162: 6526-6533, previously cited, for reasons of record, October 11, 2007.

Applicant's arguments filed April 10, 2008 have been fully considered but they are not persuasive.

Applicant indicates that there is no motivation to combine all the cited references to create a transgenic mouse expressing GNAP. Applicant indicates that this is especially true in light of the high degree of unpredictability the Examiner admits is prevalent in the present field of technology (Applicant's response, page 9). In response, as indicated in the Office Action, October 11, 2007, page 15, while an enablement rejection was written, the instant claims broadly encompass any non-human transgenic mammal carrying a GANP gene transferred thereinto, wherein said mammal has a phenotype or has no phenotype. Kuwahara et al. provide guidance that GANP was of interest and that it appeared to have a role in the cell cycle. However, not much was known about the biological role the protein had. Jaenisch was provided to teach that making transgenic overexpression animals was known in the art and that overexpression of a gene of interest would reveal not only the pathological consequences of unregulated or ectopic expression of the transgene, it will also help in the analysis of its normal function in development and differentiation. As such, guidance was provided in the art for guidance of making any transgenic animal that overexpresses a gene of interest, in order to determine what, if any, phenotype would

be exhibited by the transgenic animal that overexpresses GANP. With regard to overexpressing GANP in B cells, Maas et al. teach that a B cell specific promoter was known at the time of filing and that combining the teachings of Kuwahara et al., Jaenisch, and Maas et al. an artisan would have overexpressed GANP to see what would happen in B cells that overexpress GANP. While Applicant indicates that there is a high degree of unpredictability taught in the art, with regard to transgenic animals, the Enablement rejection indicates that this is in regard to making a transgenic animal that exhibits a phenotype related to the gene of interest. The non-human transgenic mammals recited in the claims exhibit the phenotype that GANP is overexpressed. This does not overcome the rejection at hand because any transgenic mouse can be made to overexpress a gene a gene of interest.

Applicant indicates that the Examiner is combining unrelated references in an attempt to establish a prima facie case of obviousness. References cannot be arbitrarily combined (Applicant's response, page 10). In response, Jaenisch teach that transgenic animals that overexpress a gene of interest are made in the art because they can provide guidance of the consequence of overexpression of unregulated or ectopic expression of the transgene. Nothing in the claims limits what, if any, phenotype(s) the claimed animals exhibit, except that the claimed animals overexpress GANP. These limitations are taught by Jaenisch, Kuwahara et al., and Maas et al. and thus, the combined teachings would render the claims obvious.

Applicant indicates that hypothetical embodiments are being generated here to achieve the present invention when the Examiner is taking only pieces of each

reference and disregarding other essential disclosures of the reference (Applicant's response, page 10). In response, as indicated in the Office Action, page 15, the Examiner has considered the issues of Enablement. However, the 103 was written because the art provides guidance for making any transgenic animal overexpressing a gene of interest, regardless of what phenotype the animal exhibits. As such, the combined teachings of Kuwahara et al., Jaenisch, and Maas et al. can be applied to the instant claims.

Applicant indicates that the Examiner is using impermissible hindsight (Applicant's response, pages 10-11). In response, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re McLaughlin 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). As indicated in the 103 rejection, October 11, 2007, it was known how to make transgenic overexpression animals and it was known that overexpression animals could provide insight to a gene's function when it was overexpressed. While the Enablement rejection has indicated an unpredictability in making transgenic animals, the Office Action had indicated that the 103 was written to indicate that the instant claims encompassed transgenic non-human mammals that overexpressed GANP and exhibited any or no phenotype. The instant claims still encompass transgenic non-human mammals that exhibit no or any phenotype, as long as they express GANP. Jaenisch, Kuwahara et al., and Maas et al. provide teachings

for an artisan to arrive at a transgenic overexpression GANP mouse such that the claims are obvious.

Thus, the claims remain rejected.

Claims 1, 17-19 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Kuwahara et al., 2000, Blood, 95: 2321-2328, previously cited, in view of Jaenisch, 1988, Science, 240: 1468-1474, previously cited, Maas et al., 1999, The Journal of Immunology, 162: 6526-6533, previously cited, Henderson et al., 1998, Annu. Rev. Immunol. 16: 163-200.

As discussed above, Kuwahara et al., Jaenisch, and Maas et al. provide guidance for an artisan to make a transgenic non-human animal that overexpresses GANP in B cells. While Kuwahara et al., Jaenisch, and Maas et al. provide this guidance, they do not teach the use of a human IgG enhancer.

At the time of filing, the art teaches that various Ig genes are expressed in B cells (Henderson et al., page 166, 1st parag. under "Expression and Rearrangement of Immunoglobulin Genes"). Because the CD19 promoter taught by Maas et al. contains a B cell expression specific element, an artisan would have been as likely to use the CD19 promoter or an Ig enhancer to express GANP in B cells. With regard to the claims being drawn to the use of a human IgG enhancer, using a human IgG enhancer would have been a matter of design choice.

Thus, the claims are obvious.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Art Unit 1632